3.3.2 Investigator Reported Bleeding Events: In all studies included in the ISS database, investigators rated bleeding complications (as well as other adverse events) as life threatening/severe, moderate, or mild.
The incidence of bleeding events rated as severe by the investigator is the same in the Integrilin- and placebo-treated groups (approximately 2.0%). The frequency of bleeding events rated as mild and moderate was higher in the Integrilin-treated group than in the placebo group.
There were fewer bleeding events reported in UA/NQMI patients than in patients undergoing coronary angioplasty.

The results of these ratings are shown in Table 6-4.

Table 6-4

Investigator Ratings of Bleeding Event Severity Occurring at Any Time by Indication and Treatment Group*

Investigator Rating of Severity of Bleeding Events	Coronary Angioplasty Studies				Unstable Angina Studies				All Studies			
	Integrelin (N=2736)		Placebo (N=1348)		Integrelin (N=203)		Placebo (N=107)		Integrelin (N=2939)		Placebo (N=1455)	
	N	%	N	%	N	%	N	%	N	%	N	%
Severe	56	2.0	28	2.1	4	2.0	1	0.9	60	2.0	29	2.0
Moderate	289	10.6	97	7.2	6	3.0	3	2.8	295	10.0	100	6.9
Mild	1478	54.0	651	48.3	36	17.7	14	13.1	1514	51.5	665	45.7
Missing	2	0.1	1	0.1	2	1.0	1	0.9	4	0.1	2	0.1
Patients Without Bleeding Event	911	33.3	571	42.4	155	76.4	88	82.2	1066	36.3	659	45.3

*Percentages based on total number of patients

3.3.3 Intracranial Bleeding Events: Four intracranial bleeding events were reported in patients treated with Integrilin and included in the ISS database. All four events occurred in patients undergoing coronary angioplasty. There was one intracranial bleeding event reported in a placebo-treated patient undergoing coronary angioplasty.
The incidence of intracranial bleeding in patients undergoing coronary angioplasty in the ISS database treated with Integrilin was 0.15% (4/2736) compared to 0.07% (1/1348) in placebo-treated patients.
No intracranial bleeding events were reported in the studies of patients with UA/NQMI. In addition, one intracranial bleeding event was reported in an Integrilin and Activase™ (alteplase) treated patient in the study of patients with acute myocardial infarction (IMPACT AMI, Study 92-011).

3.4 Non-Bleeding Adverse Events in the ISS Database: Common adverse events were defined as occurring at a frequency of greater than or equal to 2.0% in either the Integrilin-treated group or the placebo group. Adverse events that were reported at a frequency of less than 2% were reviewed to identify unusual but potentially serious adverse events (e.g., intracranial bleeding events). Because MI was evaluated as a clinical endpoint, it is not included as a common adverse event. The most frequently reported non-bleeding adverse events were those potentially related to an angioplasty procedure or the underlying disease. These events were reported at similar rates in both the Integrilin- and the placebo-treated patients. Hypotension and discomfort at the vascular access site were significantly more common in patients receiving Integrilin and were likely due to bleeding rather than to a an independent effect of Integrilin therapy.

To determine any possible relationships among the three most commonly reported adverse events and the incidence of bleeding associated with treatment with Integrilin in the IMPACT II study, the distribution of bleeding status was analyzed by the presence of hypotension, back pain, and injection site reaction.
The incidences of hypotension and, to a lesser extent, injection-site reaction increased with increasing severity of CEC-adjudicated bleeding in all three treatment groups suggesting that these two adverse events may be related, at least in part, to the bleeding.

The frequency of non-bleeding adverse events in patients with UA/NQMI was less than half of the frequency of adverse events in the overall ISS database. A total of 71 adverse events were reported in the Integrilin-treated patients (35.0%) and 35 (32.7%) events were reported in the placebo patients. Although they occurred at a lower frequency, the distribution of non-bleeding adverse events in the UA/NQMI studies were similar to those in the overall ISS database.
Back pain was less frequent in the Integrilin-treated or placebo-patients with UA/NQMI as patients with UA/NQMI were confined to bed rest less often than patients undergoing coronary angioplasty. Reflecting the lower incidence of bleeding events in patients with UA/NQMI, hypotension was uncommon, with only two patients (Integrilin-treated) having this adverse event.

Non-bleeding adverse events unrelated to underlying cardiac disease occurring more often in Integrilin patients than placebo patients were back pain (5.4% vs 1.9%), headache (13.8% vs 6.4%), nausea/vomiting (3.9% vs 0.0%). Higher cumulative doses and longer durations of treatment were used in the patients with UA/NQMI.

The common adverse events are summarized in Table 6-11.

Table 6-11

Frequency Of Most Common Non-Bleeding Adverse Events (>2%) Occurring at Any Time

Body System / Adverse Event	Coronary Angioplasty Studies				Unstable Angina Studies				Total			
	Integrelin N=2736		Placebo N=1348		Integrelin N=203		Placebo N=107		Integrelin N=2939		Placebo N=1455	
	N	%	N	%	N	%	N	%	N	%	N	%
ANY NON BLEEDING ADVERSE EVENT	2315	84.6	1100	81.6	71	35.0	35	32.7	2386	81.2	1135	78.0
ANY CARDIOVASCULAR EVENTS	1311	47.9	622	46.1	27	13.3	17	15.9	1338	45.5	639	43.9
Chest Pain/Angina	755	27.6	378	28.0	12	5.9	9	8.4	767	26.1	387	26.6
Hypotension	575	21.0	228	16.9	2	1.0	0	0.0	577	19.6	228	15.7
Bradycardia	143	5.2	69	5.1	1	0.5	0	0.0	144	4.9	69	4.7
Atrial Fibrillation	62	2.3	41	3.0	1	0.5	0	0.0	63	2.1	41	2.8
Hypertension	59	2.2	29	2.2	0	0.0	0	0.0	59	2.0	29	2.0
ANY DIGESTIVE	745	27.2	360	26.7	14	6.9	4	3.7	759	25.8	364	25.0
Nausea/Vomiting	653	23.9	317	23.5	8	3.9	0	0.0	661	22.5	317	21.8
Dyspepsia	65	2.4	31	2.3	2	1.0	3	2.8	67	2.3	34	2.3
ANY NERVOUS	347	12.7	157	11.6	12	5.9	5	4.7	359	12.2	162	11.1
Anxiety	83	3.0	47	3.0	2	1.0	0	0.0	85	2.9	41	2.8
Nervous/Agitated	81	3.0	32	2.4	0	0.0	0	0.0	81	2.8	32	2.2
Abnormal Thinking	56	2.0	35	2.6	4	2.0	4	3.7	60	2.0	39	2.7
ANY GENERAL BODY	1820	66.5	868	64.4	40	19.7	15	14.0	1860	63.3	883	60.7
Back Pain	1392	50.9	643	47.7	11	5.4	2	1.9	1403	47.7	645	44.3
Headache	411	15.0	215	15.9	28	13.8	9	8.4	439	14.9	224	15.4
Fever/Chills	279	10.2	145	10.8	1	0.5	2	1.9	280	9.5	147	10.1
Pain	244	8.9	119	8.8	3	1.5	0	0.0	247	8.4	119	8.2
Discomfort at Injection Site	252	9.2	99	7.3	0	0.0	0	0.0	252	8.6	99	6.8
Abdominal Pain	89	3.3	57	4.2	4	2.0	0	0.0	93	3.2	57	3.9

3.5 Deaths: The most frequent causes of death were related to the underlying cardiovascular disease. The clinical studies included in the ISS database showed an overall incidence of death at 30 days from enrollment of 0.9% (39/4394) which included an incidence of 0.8% (23/2939) in Integrilin-treated patients and 1.1% (16/1455) in placebo-treated patients (table 6-13). There was a total of 43 deaths reported after 30 days from enrollment. Two of these deaths were reported as 6-month clinical endpoints in the IMPACT I study with no information on cause of death, the remaining 41 deaths occurred after 30 days during 6 month follow-up of IMPACT II study (table 6-16).

Table 6-13
Cause of Death to 30 Days from Enrollment by Indication and Treatment Group

COSTART Code	Coronary Angioplasty		Unstable Angina Studies		All Studies		
	Integrelin (N=2736)	Placebo (N=1348)	Integrelin (N=203)	Placebo (N=107)	Integrelin (N=2939)	Placebo (N=1455)	Total (N=4394)
Any Death	18	15	5	1	23	16	39
Myocardial Infarction	7	7	0	0	7	7	14
Intracranial Bleed	3	0	0	0	3	0	3
Right Heart Failure	1	0	0	0	1	0	1
Heart Arrest	0	0	1	0	1	0	1
Sudden Death	2	2	0	0	2	2	4
Ventricular Fibrillation	0	0	1	0	1	0	1
Peripheral Vascular Disease	0	0	1	0	1	0	1
Shock	0	1	0	1	0	2	2
Other	5	5	2	0	7	5	12

Table 6-16
Patient Deaths from 30 Days Through 6 Months in the IMPACT II Study

CEC Information	Treatment Group		
	High Dose (N=1286)	Low Dose (N=1300)	Placebo (N-1285)
Cause of Death	N=10	N=17	N=14
Sudden Death	3	7	2
MI	1	4	4
Noncardiac medical/procedural	1	2	2
CHF	3	0	1
Other	2	4	5

Table 6-14 describes the patient deaths that occurred up to 30 days from enrollment.

Table 6-14
Patient Deaths to 30 Days from Enrollment in the ISS Database

Treatment Group	Patient ID	Gender/Age/ Weight	Study Drug Infusion Duration	Time from Enrollment to Death	Cause of Death
Integrelin	91-007B-10017	Male/57/97.2	48.4	2	Ventricular Fibrillation
	91-007B-12008	Male/74/65.4	72.0	-	-
	92-009-04009	Male/71/79.1	5.0	6	Intracranial Hemorrhage
	92-010A-25003	Male/65/68.0	17.8	4	During or post cardiac surgery
	93-014-14011	Female/77/95.0	24.7	14	Sudden Death
	93-014-19049	Male/66/93.0	0.7	2	Definite MI
	93-014-23039	Male/61/77.0	15.6	2	Intracranial Hemorrhage
	93-014-34072	Male/77/65.0	10.1	8	Other (Lobar Pneumonia ARDS)
	93-014-44016	Male/63/77.0	8.5	1	Definite MI
	93-014-48029	Male/62/75.0	24.1	2	Noncardiac (Respiratory Failure)
	93-014-49050	Female/71/56.0	0.7	2	Definite MI
	93-014-54012	Male/75/119.0	24.1	2	Intracranial Hemorrhage
	93-014-61034	Female/72/105.0	21.2	3	Definite MI
	93-014-82001	Female/60/67.8	23.6	16	Sudden Death
	93-014-83004	Male/68/96.0	24.0	4	Congestive Heart Failure
	93-014-84031	Female/72/97.0	11.4	1	Definite MI
	93-014-86061	Male/60/77.5	21.8	7	Other (Rupture AAA)
	93-014-91007	Male/67/88.0	0.8	0	During or post cardiac surgery
	93-014-94009	Male/59/74.0	22.9	30	Definite MI
	93-014-94021	Male/45/95.0	24.3	4	Unknown
	93-014-97004	Female/63/77.0	9.5	11	Possible MI
	93-015-56504	Female/83/43.8	19.4	2	Peripheral Vascular Disease
	93-015-62537	Male/69/83.1	12.6	12	VF Arrest
Placebo	92-009-05015	Male/79/86.0	1.3	0	Shock
	93-014-27007	Male/53/101.0	18.8	1	During or post cardiac surgery
	93-014-27060	Male/57/81.3	23.6	5	Noncardiac (Respiratory Coagulopathy, DIC)
	93-014-33015	Female/63/44.0	1.3	2	Noncardiac medical/procedural
	93-014-49045	Female/59/72.0	0.4	1	Definite MI
	93-014-55044	Female/71/77.1	19.2	2	Definite MI
	93-014-58016	Male/69/103.6	16.0	26	Noncardiac (Aspiration pneumonia)
	93-014-62008	Male/66/88.9	20.2	3	Definite MI
	93-014-62049	Male/59/67.8	20.3	6	Sudden Death
	93-014-67031	Female/82/70.8	19.8	8	Definite MI
	93-014-73024	Male/71/86.0	14.2	9	Noncardiac (Extensive thrombus)
	93-014-75012	Male/70/84.8	1.3	7	Definite MI
	93-014-84057	Female/68/80.0	23.6	1	Definite MI
	93-014-86032	Male/80/72.6	24.1	30	Sudden Death
	93-014-94034	Male/67/81.0	23.7	7	Definite MI
	93-015-47502	Male/74/68.2	18.0	29	Shock

3.6 Discontinuation due to Adverse Events: The proportion of patients discontinuing study drug because of an adverse event was higher in the Integrilin-treated group (5.4%) than in placebo group (3.5%).

Study drug discontinuation was primarily due to bleeding and cardiovascular events (similar in Integrilin-and placebo-treated patients). The most common bleeding site was the femoral artery access site. As a result, Integrilin-treated patients were more likely than placebo patients to discontinue study drug because of bleeding events at the femoral artery access site.

Table 6-17 summarizes the patients who discontinued treatment due to adverse events.

Table 6-17
Discontinuations Due to Adverse Events by Body System and Indication

Body System/ COSTART Term	Coronary Angioplasty		Unstable Angina		Total	
	Integrelin (N=2736)	Placebo (N=1348)	Integrelin (N=203)	Placebo (N=107)	Integrelin (N=2939)	Placebo (N=1455)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Any AE	148 (5.4)	43 (3.2)	10 (4.9)	8 (7.5)	158 (5.4)	51 (3.5)
Bleeding	111 (4.1)	26 (1.9)	6 (3.0)	0	117 (4.0)	26 (1.8)
Femoral Artery Access Site	85 (3.1)	14 (1.0)	0	0	85 (2.9)	14 (1.0)
Hematemesis	11 (0.4)	4 (0.3)	1 (0.5)	0	12 (0.4)	4 (0.3)
Hematuria	10 (0.4)	0	1 (0.5)	0	11 (0.4)	0
Other Bleeding	31 (1.1)	10 (0.8)	6 (3.0)	0	37 (1.2)	10 (0.8)
Whole Body	9 (0.3)	1 (0.1)	1 (0.5)	0	10 (0.3)	1 (0.1)
Cardiovascular	38 (1.4)	19 (1.4)	2 (1.0)	7 (6.5)	40 (1.4)	26 (1.8)
Digestive	9 (0.3)	0	0	0	9 (0.3)	0
Thrombocytopenia	7 (0.3)	0	0	0	7 (0.2)	0
Nervous	10 (0.4)	3 (0.2)	1 (0.5)	1 (0.9)	11 (0.4)	4 (0.3)
Respiratory	3 (0.1)	1 (0.1)	0	0	3 (0.1)	1 (0.1)
Other	3 (0.1)	0	0	0	3 (0.1)	0

3.7 Serious Adverse Events: Adverse events were reviewed to identify patients who experienced potentially serious adverse events. Events reviewed included those events identified as severe by the investigator; those that resulted in premature discontinuation of study drug, rehospitalization, or an acute medical intervention; and those unresolved at discharge. Patients with major bleeding events were also identified as having serious adverse events. In addition, laboratory data were reviewed for extreme values for platelets, creatinine, and SGPT.

In general, serious adverse events were related either to bleeding or ischemic events. Patients receiving Integrilin had a higher incidence of serious bleeding events in patients undergoing coronary angioplasty (7.2% versus 6.3%) as well as in patients with UA/NQMI (4.4% versus 0.9%). In patients undergoing coronary angioplasty, bleeding at the femoral artery access site accounted for most serious bleeding events and occurred more often in the Integrilin- than placebo-treated groups. The incidence of serious non-bleeding adverse events was similar among Integrilin- and placebo-treated patients.

The most common serious adverse events are summarized in table 6-18.

Table 6-18
Serious Adverse Events Occurring at Any Time

Adverse Event	Coronary Angioplasty				Unstable Angina				Total			
	Integrelin (N=2763)		Placebo (N=1348)		Integrelin (N=203)		Placebo (N=107)		Integrelin (N=2939)		Placebo (N=1455)	
	N	%	N	%	N	%	N	%	N	%	N	%
Any Serious Adverse Event	917	33.5	453	33.6	18	8.9	6	5.6	935	31.8	459	31.5
Any Serious Bleeding Event	196	7.2	85	6.3	9	4.4	1	0.9	205	7.0	86	5.9
Femoral Artery Access Site	132	4.8	50	3.7	0	0	0	0	132	4.5	50	3.4
CABG-Related	41	1.5	28	2.1	1	0.5	0	0	42	1.4	28	1.9
Serious Non-Bleeding Adverse Event												
Any Whole Body System	41	1.5	22	1.6	0	0	0	0	41	1.4	22	1.5
Any Cardiovascular System	763	27.9	398	29.5	12	5.9	5	4.7	775	26.4	403	27.7
Chest Pain / Angina	695	25.4	355	26.3	2	1.0	0	0	697	23.7	355	24.4
Myocardial Infarction	82	3.0	54	4.0	6	3.0	3	2.8	88	3.0	57	3.9
Any Nervous System	35	1.3	23	1.7	1	0.5	0	0	36	1.2	23	1.6
Stroke	16	0.6	8	0.6	1	0.5	0	0	17	0.6	8	0.5
Thinking Abnormality	10	0.4	4	0.3	0	0	0	0	10	0.3	4	0.3
Any Respiratory System	33	1.2	18	1.3	0	0	0	0	33	1.1	18	1.2
Respiratory Distress	14	0.5	9	0.7	0	0	0	0	14	0.5	9	0.6

4.0 Clinical Laboratory Evaluation:

Four potential areas of concern based on results from preclinical studies and the known action of Integrilin were studied in details: decrease in platelet count and thrombocytopenia; decrease in hematocrit and/or hemoglobin related to bleeding events; liver function; and renal function. However, all laboratory parameters were included in the ISS database and reviewed for evidence of Integrilin-related effects. Other than decreases in hemoglobin and hematocrit in Integrilin-treated patients consistent with the increase in minor bleeding, there was no other evidence of treatment related changes found during analysis of any laboratory parameter. No differences across the various populations were observed.

4.1 Clinical Laboratory Parameters: Baseline means and maximum mean changes from baseline for hemoglobin and hematocrit for the ISS database are summarized in Tables 7-1 and 7-2.

Table 7-1

Mean at Baseline and Mean Change from Baseline for Hemoglobin

Hemoglobin (g/dl)	Coronary Angioplasty Studies		Unstable Angina Studies		Total	
	Integrelin	Placebo	Integrelin	Placebo	Integrelin	Placebo
Baseline						
N	2651	1299	199	102	2850	1401
Mean	13.9	13.9	13.2	13.4	13.9	13.9
SD	1.48	1.46	1.82	1.62	1.51	1.48
Range	8.3-18.5	6.4-19.0	7.0-16.6	9.6-16.5	7.0-18.5	6.4-19.0
Maximum Change from Baseline*						
N	2605	1273	197	101	2802	1374
Mean	-1.2	-1.0	-0.8	-0.7	-1.1	-1.0
SD	2.13	1.97	1.41	1.26	2.09	1.92
Range	-9.7-58.8	-8.5-26.5	-5.0-3.1	-4.7-2.2	-9.7-58.8	-8.5-26.5

* Or first time point after treatment termination

Table 7-2

Mean at Baseline and Mean Change from Baseline for Hematocrit

Hematocrit (%)	Coronary Angioplasty Studies		Unstable Angina Studies		Total	
	Integrelin	Placebo	Integrelin	Placebo	Integrelin	Placebo
Baseline						
N	2651	1299	198	102	2849	1401
Mean	41.0	41.0	39.0	39.5	40.8	40.9
SD	4.18	4.17	5.04	4.51	4.28	4.21
Range	25.4-53.1	26.3-55.0	21.2-50.1	29.9-48.4	21.2-53.1	26.3-55.0
Maximum Change from Baseline*						
N	2606	1273	196	101	2802	1374
Mean	-3.3	-2.9	-2.2	-2.2	-3.2	-2.9
SD	5.50	5.52	4.30	3.75	5.43	5.41
Range	-36.7-17.6	-30.6-11.5	-15.0-8.5	-14.6-5.7	-36.7-17.6	-30.6-11.5

* Or first time point after treatment termination

Overall, there was no evidence of a drug-related effect on platelet counts. Significant decreases in platelet counts occurred with similar frequency in Integrilin- and placebo-treated groups.

Although thrombocytopenia as a subjective report was "more frequent" with Integrilin than placebo in the IMPACT II study (0.6% vs 0.2% vs 0% in the high-dose, low-dose, and placebo groups, respectively), examination of laboratory data (nadir counts, proportion of patients with counts less than 100,000/mm^3 or less than 50,000/mm^3) failed to reveal objective evidence of a real difference in platelet counts between active drug and placebo during infusion and afterward until patients left the hospital.

The mean baseline platelet counts and mean changes from baseline for platelets are summarized in table 7-3 and the marked abnormalities for platelet by treatment are summarized in table 7-4.

Table 7-3

Mean at Baseline and Mean Change from Baseline for Platelets

Platelets (K/mm3)	Coronary Angioplasty Studies		Unstable Angina Studies		Total	
	Integrelin	Placebo	Integrelin	Placebo	Integrelin	Placebo
Baseline						
N	2649	1297	198	101	2847	1398
Mean	235.0	234.5	255.5	249.0	236.4	235.5
SD	63.18	63.82	81.02	63.22	64.77	63.87
Range	85.0-787.0	97.0-575.0	103.0-874.0	120.0-479.0	85.0-874.0	97.0-575.0
Maximum Change from Baseline*						
N	2645	1293	197	101	2842	1394
Mean	-8.2	-10.9	-16.6	-14.7	-8.8	-11.2
SD	70.0	72.75	64.81	46.62	69.67	71.17
Range	-374.0-543.0	-276.0-419.0	-621.0-152.0	-117.0-198.0	-621.0-543.0	-276.0-419.0

* Or first time point after treatment termination

Table 7-4

Summary of Marked Abnormalities for Platelets by Treatment Group

Post-Baseline Platelet Abnormality	Coronary Angioplasty				Unstable Angina				All Studies			
	Integrelin (N=2736)		Placebo (N=1348)		Integrelin (N=203)		Placebo (N=107)		Integrelin (N=2939)		Placebo (N=1455)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<100,000/mm^3	71	(2.6)	31	(2.3)	3	(1.5)	0		74	(2.5)	31	(2.1)
50% drop from BL	62	(2.3)	38	(2.8)	2	(1.0)	1	(0.9)	64	(2.2)	39	(2.7)
<50,000/mm^3	7	(0.3)	8	(0.6)	0		0		7	(0.2)	8	(0.5)

There was no evidence of a drug-related effect of Integrilin on LFTs. Mean and median values of SGOT and SGPT, changes from baseline and marked abnormalities were similar for Integrilin- and placebo-treated groups.
No significant abnormalities were noted for alkaline phosphatase

There was no evidence of an effect of treatment with Integrilin on renal function.

4.2 Immunogenicity of Integrilin: The potential for this disulfide-linked cyclic heptapeptide to produce an immune response in humans was addressed in three separate clinical studies in a total of 390 patients. Protocol 94-019, designed to specifically study the development of anti Integrilin antibodies and allergic reactions with repeat exposure, was conducted in 28 healthy volunteers under randomized, double-blinded, placebo-controlled conditions. Twenty-one subjects received a bolus dose and infusion of Integrilin on two separate occasions separated by one month. Follow-up examinations for the presence of anti-Integrilin antibodies were conducted up to 16 weeks after the initial exposure.
In Protocol 92-009, 22 patients had blood samples drawn for the detection of antibodies to Integrilin at baseline and at the 30-day assessment.
In the IMPACT II Study, the first ten patients enrolled at each site were tested for the presence of Integrilin antibodies at the 30-day assessment.

There was no evidence of immunogenic response to Integrilin: no anti-Integrilin antibodies were detected in 390 patients and no serious adverse events occurred with repeat administration of Integrilin 30 days apart. Repeat dosing gave similar plasma drug concentrations and inhibition of platelet aggregation.

5.0 Drug Interactions

5.1 Drug-Drug Interaction: No evidence of a pharmacokinetic interaction was observed in Phase I and II studies with the administration of Integrilin plus ASA and/or heparin. Simplate bleeding times were modestly increased in the presence of Integrilin, heparin had no additive effect.
A population pharmacokinetics study was conducted within the IMPACT II study, where 1725 treated patients had a single plasma Integrilin concentration determined prior to terminating the infusion. Although plasma Integrilin clearance appeared to be affected by age, weight and renal function, it was not found to be affected by the co-administration of any of the cardiac drugs which were coadministered during the study, and which represent the medications most likely to be administered in the target population, including beta-blockers, calcium channel blockers, diuretics, heparin.

The effect of concomitant administration of other known antithrombotic agents was examined in detail in the IMPACT II study. Table 10-2 summarizes major and minor bleeding events by concomitant medications.

Table 10-2
Incidence of CEC-Adjudicated Major and Minor Bleeding by Subgroup* and Treatment Group in the IMPACT II Study

CEC Bleeding By	Integrelin High Dose		Integrelin Low Dose		Placebo	
	Major	Minor	Major	Minor	Major	Minor
Warfarin	12/105 (11.4%)	26/105 (24.8%)	13/130 (10.0%)	27/130 (20.8%)	17/153 (11.1%)	44/153 (28.8%)
No Warfarin	46/1140 (4.0%)	151/1140 (13.2%)	42/1119 (3.8%)	119/1119 (10.6%)	38/1077 (3.5%)	71/1077 (6.6%)
Warfarin and PT ≤14.5 sec	11/96 (11.5%)	25/96 (26.0%)	10/114 (8.8%)	25/114 (21.9%)	14/127 (11.0%)	37/127 (29.1%)
Warfarin and PT >14.5 sec	0/4 (–)	0/4 (–)	2/9 (22.2%)	1/9 (11.1%)	0/14 (–)	4/14 (28.6%)
Dipyridamole	17/189 (9.0%)	38/189 (20.1%)	14/180 (7.8%)	33/180 (18.3%)	18/191 (9.4%)	35/191 (18.3%)
No Dipyridamole	41/1056 (3.9%)	139/1056 (13.2%)	41/1069 (3.8%)	113/1069 (10.6%)	37/1039 (3.6%)	80/1039 (7.7%)
Thrombolytics	1/15 (6.7%)	4/15 (26.7%)	2/15 (13.3%)	4/15 (26.7%)	2/23 (8.7%)	5/23 (21.7%)
No Thrombolytics	57/1230 (4.6%)	173/1230 (14.1%)	53/1234 (4.3%)	142/1234 (11.5%)	53/1207 (4.4%)	110/1207 (9.1%)

* In each category, denominator is total number of patients with CEC bleeding status determined.

5.2 Drug-Demographic Interaction: In the IMPACT II study, an increase of 10 kg in weight from the median of 84 kg was associated with an increase of 5.9% in the estimated mean plasma Integrilin clearance of 158 mL/min. Also, an increase of 10 years in age from the median of 60 years was associated with a 5.3% decrease in Integrilin clearance.

In the younger subjects enrolled in most Phase I studies, estimates for plasma clearance were also consistently higher and had a half-life shorter compared to the older patients enrolled in Phase II studies or the four healthy, but older, post-menopausal women studied in Phase I.

The population pharmacokinetics analysis in IMPACT II did not reveal any notable influence of gender, inadequate data were available for non-Caucasian to assess the influence of ethnic origin. Major bleeding was inconsistently correlated with increasing age, except that the highest incidence was noted in patients > 70 years of age in the high dose Integrilin group (7.1%). Minor bleeding was correlated with increasing age, and older patients treated with Integrilin were at higher risk compared to placebo treated patients. Patients weighing < 74 kg had an increased incidence of minor bleeding and this risk was increased by Integrilin. In the high

dose Integrilin group, patients weighing < 74 kg also had an increased incidence of major bleeding. Women had an increased incidence of minor bleeding compared to men, and this risk was increased by Integrilin. Women in the high dose Integrilin group also had an increased risk of major bleeding. Part of this risk is attributable to weight differences between men and women.
Overall, there was no consistent evidence of a difference in the effect of Integrilin relative to placebo among the subgroups for non-bleeding adverse events.

5.3 Drug-Disease Interaction: In the IMPACT II study, one of the patients with creatinine >2.0 mg/dL in the high dose group experienced an intracranial bleed during the infusion period. The patient had also uncontrolled hypertension. Other adverse events experienced by this group of patients were similar to those of the general patient population. Additionally, there were no clinically relevant changes in laboratory values following treatment for these patients.

Integrilin is intended as an acute-care product (up to 72 hours of exposure), no long-term use is anticipated. Due to the short half-life of Integrilin (about 2 hours), no long-term adverse effects are expected to be associated with treatment.

6.0 Dosing Safety

The number of patients and adverse event rates in Phase I and Phase II studies not included in the ISS database were too low to allow meaningful conclusions regarding the relationship between drug exposure and adverse events.
The vast majority of patients included in the ISS analysis are derived from the 94-014 (IMPACT II) study.

Table 13-1 shows the occurrence of bleeding by cumulative exposure to Integrilin.

Table 13-1
Bleeding Events by TIMI Criteria by Cumulative Dose in ISS Database

TIMI Classification	Total Cumulative Dose of Integrelin (µg/kg)									
	≤ 700		700-850		850-1000		1000-1150		≥ 1150	
	N	%	N	%	N	%	N	%	N	%
Major	58	14.6	19	2.2	12	2.8	17	3.0	18	2.9
Minor	88	22.2	86	10.0	47	11.1	66	11.5	73	11.8
Insignificant	118	29.7	428	49.8	216	50.9	292	51.0	268	43.3
None	119	30.0	290	33.7	136	32.1	183	31.9	249	40.2

The expected cumulative drug exposures for a 20-24 hour infusion (including bolus) are 735-855 µg/kg and 1035-1215 µg/kg for the 0.5 µg/kg-min and 0.75 µg/kg-min groups, respectively.

The cumulative dose represents a measure of the dose level (0.5 mg/kg-min versus 0.75 mg/kg-min) and the duration of the infusion. The greater frequency of major and minor bleeding events or non-bleeding events in patients having received $\leq$700 ug/kg of drug likely reflects its premature discontinuations presumably due to bleeding or other adverse events, rather than an inverse relationship between dose and bleeding frequency. Greater cumulative exposures to Integrilin were not associated with a greater incidence of bleeding event.

6.1 Overdose: This included large bolus doses, rapid infusion reported in the CRF as "overdose", and large cumulative doses. None of the three patients receiving large bolus dose had significant adverse events or changes in laboratory values. There were 10 reports of accidental "overdosage" in the IMPACT II study, 8 in the Integrilin groups (5 high dose, 3 low dose) and 3 in the placebo group. None of these patients received twice the recommended bolus dose or infusion rate. None of these patients had a serious adverse event or more than mild bleeding (usually at the access site). Plasma levels of Integrilin, available for 7 of the 8 patients, were similar to the mean levels for patients dosed properly. Two patients in the high-dose Integrilin had high plasma levels after receiving rapid infusion rates, with no apparent effect. The safety profiles of 3 patients who received a total cumulative dose of over 5000 mg/kg showed no adverse events or laboratory values.

6.2 Withdrawal Effects: Because Integrilin is intended for use a an acute-care product, effects of withdrawal are not anticipated. Adverse events in the IMPACT II study reported as occurring between 24 hours post-treatment and 30 days post-randomization were similar between Integrilin-treated and placebo-treated patients. There are no known effects of withdrawal associated with the use of Integrilin.

7.0 Safety Update (4 month)

A 4 month safety update was submitted on 8-2-1996. No additional studies in PTCA patients had been performed. One Phase III study in UA (PURSUIT) is ongoing and still blinded. One Phase II study in acute MI has been completed, but the final analysis is not yet completed. Both studies employed dose regimens of Integrilin different from those used in the IMPACT II study. The data reported for the safety update reflect the different dose regimens and the different patient populations, however, no unexpected adverse events were reported.

CONCLUSIONS

Integrilin is a cyclic peptide with selective and reversible binding affinity to the GPIIb/IIIa platelet receptor complex. Integrilin inhibits platelet aggregation independently of the inducing mechanism because it prevents the ultimate, common pathway of fibrinogen binding to the platelet receptor GPIIb/IIIa. The effect of Integrilin on platelet is immediate, rapidly reversible and limited primarily to the period of its administration. Integrilin has been developed as an antithrombotic agent for the treatment of acute coronary syndromes where local thrombus formation plays a major pathogenetic role.

A New Drug Application (NDA 20-718) has been submitted by COR Therapeutics, Inc. for the approval of Integrilin as an adjunct therapy in patients undergoing percutaneous transluminal coronary angioplasty, atherectomy, excimer laser or rotoblator (PTCA) for the prevention of acute cardiac ischemic complications (death, MI, need for urgent intervention) related to abrupt closure of the treated coronary vessel.

A single adequate and well controlled Phase III clinical trial, the IMPACT II study, has been submitted in the NDA to provide substantial evidence of the efficacy and safety of Integrilin in preventing the acute ischemic complications of coronary angioplasty. IMPACT II is a large, randomized, multi-center, double-blind clinical trial of 4010 patients undergoing urgent or elective PTCA at 83 centers in the US. The study design had minimal exclusion criteria allowing a broad cross-section of the population to be studied. The large study population adequately represented the target population for the proposed indication. Randomization and blinding to treatment assignment were adhered to throughout the study.
Some discrepancies in the data reported in the NDA were noted during the review, however, they did not seem to affect the final interpretation of the study results. The results were not determined by any study center in particular and there was no evidence of selection bias.

Two dosing regimens of Integrilin, 135 ug/kg bolus followed by infusion of 0.75 ug/kg/min for 20-24 hours and 135 ug/kg bolus followed by 0.50 ug/kg/min infusion for 20-24 hours (referred to as"high-dose" and "low-dose", respectively,) were each compared to placebo, allowing for internal replication of results.

The primary efficacy endpoint specified in the study protocol was the composite occurrence of death, myocardial Infarction and/or urgent coronary intervention. The components of the composite endpoint were adjudicated by an independent, blinded clinical events committee (CEC) according to protocol-

specified definitions. Clinical events were also evaluated according to the investigators' assessment as reported in the CRFs.

The primary assessment was at 30 days from randomization in order to determine whether the benefits from Integrilin administration were sustained beyond the periprocedural period. Efficacy was also assessed at 24 and 48 hours from randomization when the risk of abrupt closure and acute ischemic events is highest. Pre-specified secondary endpoints included rates of abrupt closure and clinical events at 6 months.

Two pre-specified data sets were analyzed: the randomized and the treated patient populations. A total of 139 from the 4010 randomized patients (3.5%) did not receive study medication because randomization was assigned before the eligibility of the patient was established or before the decision to treat the patient or to proceed with angioplasty could be made by the investigator. These 139 untreated patients were evenly distributed across the three study groups, were randomized at more than half of the study centers and were excluded from treatment by investigators who were blinded to treatment assignment. For the above reasons, the "treated patient" population was considered valid for the primary efficacy analyses. A "randomized patient" analysis was performed as well in order to provide supportive information and to check for potential selection bias.

The protocol-defined level of significance for the comparison of the composite clinical endpoint between each Integrilin group and placebo was set at the p-value $=0.035$ in order to adjust for dual pair-wise comparisons and, more importantly, for the interim analyses performed during the study. However, when fully adjusted, the p-value of 0.035 actually corresponded to an overall alpha level of 0.067. The conventional p-value of 0.05 was used for all other comparisons in this study.

The efficacy results of the IMPACT II study showed that the administration of Integrilin to patients undergoing PTCA produced a marked reduction in the incidence of acute ischemic events when compared to placebo at 24 hours post-PTCA. Both dosing regimens of Integrilin effectively reduced the incidence of the composite endpoint of death, MI and/or urgent revascularization by 28-31% compared to placebo. The reduction persisted for approximately 5 days after PTCA without evidence of rebound thrombotic events after discontinuation of study drug. In the early post-angioplasty period of greatest risk, more placebo patients discontinued study drug because of coronary occlusion than Integrilin-treated patients. The incidence of abrupt closure was reduced by 35% ($p=0.030$) in the high dose Integrilin group and by 45% ($p=0.003$) in the low dose Integrilin group compared to placebo. As expected, abrupt closure had a very high incidence of

ischemic events (>40%) compared to 10% for patients without abrupt closure.

At 30 days post-PTCA, a reduction in incidence of the composite endpoint persisted in the Integrilin groups compared to the placebo group. However, the reduction was statistically significant only In the low dose Integrilin-treated group at the nominal p-value=0.035. In this group, the risk reduction of ischemic events was 21.6% with an absolute reduction of composite endpoint of 2.5%.
No statistically significant difference was found in the high-dose Integrilin due to the occurrence of 6 additional composite endpoint between day 5 and 30 in this group compared to placebo, nor in the randomized population due to 5 composite endpoint events: 1 in the high dose group and 4 in the low-dose group.

The long-term effect of Integrilin was also assessed at 6 month post-randomization. As most revascularization procedures performed after 30 days from randomization in all treatment groups were elective, the 6-month analysis examined the composite of death and/or MI and a composite of death, MI and/or any (i.e. urgent and non-urgent) intervention. A numerical reduction in the composite endpoint events of death and MI persisted at 6 months in the Integrilin-treated patients compared to placebo. The net difference in incidence of the composite endpoint of death and MI compared to placebo was 1.3% for the low-dose and 1.6% for the high-dose Integrilin regimen.
Elective or non-urgent coronary revascularization procedures were performed throughout the study period up to 6 months post-randomization. The relative risk reduction of all events (death, MI and any revascularization procedure) in the low-dose group compared to placebo was 21.2% at 24 hours, 12.1% at 30 days, and 4.0% at 6 months. More Integrilin-treated patients had required re-hospitalization because of chest pain/angina than patients in the placebo group.

Several additional efficacy analyses were performed, including the analysis of the investigator assessed endpoints, a post-hoc comparison of the combined Integrilin treatment groups to placebo, analyses of first or most severe endpoint events, high or low risk stratification, MI subtypes, effect of investigational site.

The 30 day efficacy analysis performed according to the investigators' assessment of the composite endpoint events showed a statistically significant difference in favor of the low-dose Integrilin compared to placebo in both treated and randomized patient populations. However, the investigators and the CEC analyses were discordant in that the investigators identified considerably fewer clinical events, particularly MIs, than the CEC. The MI were classified by the CEC as Q-wave MI and small or large enzyme MI according to ECG findings and degrees of elevations of CK/CK-MB levels. The CEC identified more MIs on the basis of elevated post-angioplasty CK and CK-MB levels. Although the investigators

concurred with the CEC for the identification of large enzyme MI more frequently than for the identification of small enzyme MI, a considerable proportion of large enzyme MI were not identified by the investigators (36/53 in the high-doe group, 29/52 in the low-dose group, and 39/68 in the placebo group).

A comprehensive analysis of the results was performed to examine any patient subgroup that may experience a greater or lesser therapeutic effect from Integrilin. A numerical difference in favor of Integrilin was detected in a wide variety of subgroup analyses of efficacy. Of note is that no Integrilin-treated patient populations were identified who experienced a worse clinical outcome than the placebo group. No gender-related differences in efficacy were noted.

Sub-group analyses by risk level, stent placement, and concomitant aspirin and heparin therapy were also performed.

Integrilin-treated patients undergoing low-risk or elective PTCA (as determined by the randomization questionnaire, by the investigator assessment in CRFs, and by the EPIC criteria) experienced fewer events than patients in the high-risk stratum. However, the prospectively defined risk stratification was not predictive of outcome because no difference in incidence of events was observed between the high- and low-risk strata in the placebo-treated group at either 24 hours or 30 days.

A total of 91 patients underwent PTCA with placement of stents and continued Integrilin therapy during stent placement having been randomized to either Dextran/placebo-Integrilin or to Integrilin/placebo-Dextran. The incidence of the primary composite endpoint at 30 days for patients receiving stents was lower in the Integrilin groups than in the placebo group.

Most patients in IMPACT II received concomitant aspirin and heparin to reduce the risk of acute cardiac complications due to thrombosis. All patients in the study received at least one bolus of heparin. No consisted effect of heparin therapy duration was observed on the incidence of composite endpoint.
In the small group of patients (n = 80) who did not receive aspirin due to a contraindication, the incidence of the composite endpoint was lower in the Integrilin-treated patients.

The overall safety profile of Integrilin, at the dose regimens used in the clinical trials in the NDA, was favorable. As expected, bleeding was the most commonly reported adverse event. The great majority of bleeding events occurred at the femoral artery access site as a result of the angioplasty procedure itself. Most of the bleeding events were minor and limited to the period during which the patient was being treated. Minor bleeding was, however, more frequent with Integrilin that with placebo; a dose-response was also apparent for minor bleeding.

Moderate bleeding, including spontaneous bleeding, was more frequent in patients receiving Integrilin. In fact, more Integrilin-treated patients than placebo patients discontinued study drug due to bleeding complications.
Severe bleeding events as defined by TIMI criteria and by investigator assessment were rare and occurred with equal frequency in all groups. The overall incidence of intracranial bleeding with Integrilin was low and not higher than with placebo.
Major bleeding associated with CABG surgery was actually less common among patients receiving Integrilin.
In general, the incidence of major and minor bleeding events increased in females and with increasing age and lower body weight. Patients receiving concomitant warfarin and/or dipyridamole experienced an increased incidence of major and minor bleeding events, but Integrilin did not increase this risk.

Adverse events other than bleeding that occurred more often in the Integrilin-treated patients compared to placebo, were back pain, hypotension (secondary to bleeding) and pain at the injection site.

There was no evidence of Integrilin-related organ toxicity (liver, kidney). No adverse hematological effects, other than reduction in Hgb and Hct secondary to blood loss were detected in the Integrilin-treated patients. Inhibition of platelet aggregation induced by Integrilin does not appear to affect the viability of platelets, as demonstrated by the low overall incidence of reported thrombocytopenia, which occurred with similar frequency in all treatment groups.
The potential for thrombocytopenia was of specific concern because of the findings in one animal study of a transient dose-dependent decrease in platelet counts in female rabbits which was not reproduced in other animal studies.

Allergic reactions were rare and occurred with similar frequency in the Integrilin and placebo groups. There were no cases of anaphylaxis and no antibodies to Integrilin were detected in 412 patients 30 days after one administration and in 21 patients after repeated administrations of Integrilin.

It is of note that in IMPACT II only 44.5% of the patients in the Integrilin low-dose group (50 ug/kg-min) group and only 68.3% of the patients in the Integrilin high-dose group (0.75 ug/kg-min) had a steady-state plasma concentration of Integrilin which would have resulted in at least an 80% inhibition of ADP-induced *ex vivo* platelet aggregation. A higher dose regimen of Integrilin might reduce further the incidence of ischemic events, however, the likelihood of more clinically significant bleeding would negatively affect the risk/benefit relationship of the treatment.

In conclusion, Integrilin exhibited a marked antithrombotic effect which significantly reduced the risk of abrupt closure and related complications in the early post-PTCA period. A marginal reduction of the composite endpoint of ischemic events was sustained at 30 days in the low-dose (135 ug/kg bolus followed by a 0.5 ug/kg/min infusion of 20-24 hours) Integrilin-treated group. The clinical importance of Integrilin as an adjunct therapy for the prevention of acute ischemic complications related to abrupt closure in patients undergoing coronary angioplasty will be evaluated by the Cardio-Renal Advisory Committee.

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cc:
NDA 20-718
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